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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,361	ISLAM ET AL.	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-118* is/are pending in the application.

4a) Of the above claim(s) *99-109 and 117* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-98,110-116 and 118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 November 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of claims 63-98, 110-116, and claim 188 in part in the reply filed on 04/14/2008 is acknowledged. The traversal is on the ground(s) that that there is no lack of unity of invention as Applicant argues that Mullis et al. do not teach a common technical feature of the claims. This is not found persuasive because Mullis et al. do teach the common technical feature of the claims which is detection of double stranded target nucleic acids using primers separated on two opposite strands by 0-25 nucleotides as given in instant claim 63 (see section 2 of Office action mailed on 01/14/2008). Applicant agrees that Mullis et al. teach this common technical feature (see first full paragraph on p. 7 of Applicant's response filed on 04/04/2008). This feature is common to the claims and is not a special technical feature. The claims are not linked by a special technical feature and thus the claims lack unity of invention. Applicant also argues the Mullis et al. teach beyond the recited elements of instant claim 63 which recites a method "comprising" the recited steps and elements. First, Mullis et al. teach the recited steps and elements as already presented. Second as the claim recites "comprising", other added steps and elements given by Mullis et al. are within the scope of the claim. Applicant then further argues that Mullis et al. fail to teach limitations found in some dependent claims. Whether this is so or not is irrelevant to this lack of unity. Mullis et al. teach the common technical feature of the claims which is recited in independent claim 63.

The requirement is still deemed proper and is therefore made FINAL.

Claims 99-109 and 117 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 04/04/2008.

2. Applicant's election with traverse of the Subgroup which is the primer pair of sequences given in SEQ ID NOs: 19 and 25 in the reply filed on 05/28/2008 is acknowledged. The traversal is on the ground(s) that each primer in this pair is linear and another primer with a different SEQ ID NO. is a hair-pin. This not found persuasive as claim 98 recites that the oligonucleotides are selected from the listed SEQ ID NOs. The oligonucleotides are the two oligonucleotides of antecedent claim 63. Only two oligonucleotides are required in the methods of claims 63 and 98 and thus the requirement for two oligonucleotides is proper. Applicant also argues that this an improper specie election of a Markush group. However, the election is not of a specie but of a Subgroup. Furthermore, Applicant has failed to submit evidence or identify such evidence now of record showing the Restriction Subgroups to be obvious variants or clearly admit on the record that this is the case.

The requirement is still deemed proper and is therefore made FINAL.

The sequences of SEQ ID NOs. 10, 13 and 20, 12, 22, 23, 24, 11, 21, 26, and 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn

to a nonelected Subgroup, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 05/28/2008.

Claims 63-98, 110-116, and 118 consonant with the election of the subgroups of SEQ ID NOs: 19 and 25 are pending and at issue.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It was not executed in accordance with either 37 CFR 1.66 or 1.68. Full dates are not given for the signatures on the oath.

Drawings

4. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Figures 8-12 have sequences without SEQ ID NOs (see also Sequence Compliance below). Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Sequence Rules Compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given time of reply to this office action within which to comply with the sequence rules, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in **abandonment** of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Figures 8-12 and page 34 respectively contain sequences without SEQ ID NOs. If these sequences are included in the sequence listing provide by Applicant, the specification should be amended to include the SEQ ID NOs. If these sequences were not included in the sequence listing filed 08/12/2008, Applicant should provide a substitute sequence listing and a CRF that include those sequences.

Specification

6. The abstract of the disclosure is objected to because it does not consist of complete sentences but contains clauses without a main verb and hence is not a paragraph. Correction is required. See MPEP § 608.01(b).

Claim Objections

7. Claim 63 is objected to because of the following informalities: improper grammar in reciting " . . . detection and/or quantitation of target nucleic acid sequence . . .."; it appears that "*a* target nucleic acid sequence" is intended. Appropriate correction is required.

8. Claim 63 is objected to because of the following informalities: improper grammar in reciting " . . .carrying out denaturation step. . ."; it appears that "carrying out *a* denaturation step" is intended. Appropriate correction is required.

9. Claims 65 is objected to because of the following informalities: improper grammar in reciting " . . .carrying out denaturation step. . ."; it appears that "carrying out *a* denaturation step" is intended. Appropriate correction is required.

10. Claims 73 is objected to because of the following informalities: improper grammar in reciting " at or near 3'end "; it appears that "at or near *the* 3' end" is intended. Appropriate correction is required.

11. Claim 77 is objected to for reciting "anyone" in the preamble, it appears that "any one" is intended. Appropriate correction is required.

12. Claim 87 is objected to because of the following informalities: lack of proper identification of trademarks TEXAS RED, CY-3, and CY-5. Appropriate correction is required.

Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is advised to scan the entire application to ensure trademark usage in all the places where it appears in the application is in compliance with the current office guidelines.

13. Claim 88 is objected to because of the following informalities: lack of proper identification of trademarks PICOGREEN and YO-PRO-1. Appropriate correction is required.

Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is advised to scan the entire application to ensure trademark usage in all the places where it appears in the application is in compliance with the current office guidelines.

14. Claim 92 is objected to for reciting "translucent and glass", it appears that "translucent and is glass" is intended. Appropriate correction is required

Claim Interpretation

15. Claim 63 recites "A simple and improved method" but does not distinguish those elements, steps, and/or relationships of the claim which are improved. Thus the claim is not examined as a Jepson type claim. Should Applicant wish to distinguish what are the improvements in claim, Applicant is directed to 37 CFR 1.75(e).

Claim Rejections - 35 USC § 112, First Paragraph

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 75, 80, 94, 95, 107, and 112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims recite "not excluding others" where the "others" are not described in the specification.

18. Claim 87 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This claim recites "many other moieties" which is not described in the specification.

19. Claim 89 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This claim recites "of the like" and "other conjugates" which are not described in the specification.

20. Claim 92 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This claim recites "and the like" which is not described in the specification.

Claim Rejections - 35 USC § 112, Second Paragraph

21. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claims 63-98, 110-116 and 118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Furthermore, the claims are

generally narrative and indefinite, failing to conform with current U.S. practice. They are replete with grammatical and idiomatic errors.

23. Claims 63-98, 110-116 and 118 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: detection and/or quantitation of target nucleic acid sequence as recited in the preamble of claims 63 and 110.

24. Claim 63 recites the limitation "cycle" in line 6. There is insufficient antecedent basis for this limitation in the claim.

25. Claim 64 recites the limitation "high through put PCR" in line 4. There is insufficient antecedent basis for this limitation in the claim.

26. Claims 65 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims recite the words "at or near preferably near 3' end". These words are so grammatically incorrect that a meaning is not decipherable and thus the claims are indefinite.

27. Claim 76 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the words "at or near preferably near its 3' end". These words are so grammatically incorrect that a meaning is not decipherable and thus the claim is indefinite. The use of the pronoun "its' make the words more unclear as the antecedent of the pronoun "its" is unclear.

28. Claim 63 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: what is the selected element(s) for "at least a selective annealing step" as recited in the last line of the claim. Dependant claims 64-98, 110-116 and 118 are thus also incomplete.

29. Claim 67 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: what elements and cooperative relationship constitute "otherwise configuration".

30. Claims 65, 66, 75, 76, 82, 83, 94, 95, and 100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims recite the words "at or near preferably near 3' end". These words are so grammatically incorrect that a meaning is not decipherable and thus the claims are indefinite.

31. Claims 75 and 76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are unclear as the antecedent of the pronoun "its" is unclear. In claim 76 it is unclear as to what the third oligonucleotide is complementary to. Claim 76 omits essential elements and or steps and so that it is unclear how the third oligonucleotide gets separated.

32. Claim 75 contains the trademark/trade name DABCYL. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a quencher and, accordingly, the identification/description is indefinite. It is noted that the trademark is properly identified but the generic term, e.g. dye, is not recited with the trademark.

33. Claim 76 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the elements of the third nucleotide and/or additional essential steps for which the third oligonucleotide "gets separated" as recited in the claim.

34. Claim 87 contains the trademark/trade names FAM, JOE, TEXAS RED, DABCYL, and DABCYL derivatives. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since

the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe donors and acceptor moieties and, accordingly, the identification/description is indefinite. It is noted that some of the trademarks are properly identified but the generic term, e.g. dye, is not recited with the trademark.

35. Claim 87 contains the trademark/trade names FAM, JOE, TEXAS RED, DABCYL, and DABCYL derivatives. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe donors and acceptor moieties and, accordingly, the identification/description is indefinite. It is noted that some of the trademarks are properly identified but the generic term, e.g. dye, is not recited with the trademark.

36. Claims 82 and 83 recites the limitation "being said labeled oligonucleotide primer pairs" in lines 9 and 10 respectively. There is insufficient antecedent basis for this limitation in the claims. Furthermore, the claim seems to intend that both oligonucleotides are labeled then later recites that the second oligonucleotide (termed a primer) is unlabeled. It is unclear as to what method this claim is intending to recite. Thus these claims have been interpreted as reciting two oligonucleotides, one of which is labeled.

37. Claim 84 recites the limitation "the labeled oligonucleotides" in lines 2 and 3. There is insufficient antecedent basis for this limitation in the claim.

38. Claim 84 recites the limitation "the detectable signal" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 92 is indefinite for reciting glass or plastics like . . . dextran. Dextran is a sugar and is neither a glass or plastic. It is uncertain how dextran relates to the recited method.

39. Claim 118 is indefinite as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claim does not recite any active method step or kit components.

While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d, p. 1011 (Bd. Pat. App. Int. 1986). It is suggested that the claims be rewritten such that they set forth defined methods, such as by reciting "[a] method of..., comprising the steps of ...", after which a series of active steps is recited, for example “amplifying a target nucleic

acid . . ." and "detecting the target nucleic acid . . . ". If a kit is contemplated, it is suggested that one or more components or reagents be recited, and applicant is reminded that examination is based only on such components or reagents and not on how the kit is intended to be used.

Claim Rejections - 35 USC § 102

40. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

41. Claims 63-92, 96, 97, and 110-116 and 118 are rejected under 35 U.S.C. 102(b) as being anticiapted by Nazarenko et al. (United States Patent 6,117,635 issued September 12, 2000).

Regarding claims 63, 66, 82, 85, 86, 90, and 118, Nazarenko et al. teach simple and improved methods of detection and/or quantitation of target nucleic acid sequence (entire patent) comprising:

(i) providing at least two oligonucleotides as a pair of primers for amplification of said target sequence by teaching:

> "The invention provides a method for detecting or measuring a product of a nucleic acid amplification reaction comprising: (a) contacting a sample comprising nucleic acids with at least two oligonucleotides, a first one of said oligonucleotides comprising a sequence complementary to a preselected target sequence that may be present in said sample, and said first one and a second of

> said oligonucleotides being a pair of primers adapted for use in said amplification reaction . . . " (see column 13 lines 27-34),
>
> "In another embodiment, the donor moiety is located on a first oligonucleotide and the acceptor is located on a second oligonucleotide" (see column 16 lines 23-26),
>
> and teach that the donor and acceptor can be MET moieties and FRET moieties which are a type of MET moieties and teach the MET/FRET distance is 10-100 Angstrom (see column 1 lines 14-16 lines 30-56) which is within the range of 10-80 Angstrom,
>
> and teach: "The target nucleic acid can be genomic or cDNA or mRNA or synthetic, human or animal, or of a microorganism . . (see column 20 lines 3-5);

(ii) subjecting the target sequence to amplification such that the 3' ends of said pair of primers are on two opposite strands and separated from one another by 0-25 nucleotide pairs in the final amplification product by teaching a target sequence which is 18 nucleotides of the 18 nucleotide double strand pairs with primer oligonucleotides on opposite strands and thus having a 3' end separation of 18 nucleotide pairs which is within the range of 0 to 25 nucleotide base pairs (see Example 10) and also teaching as follows:

> " Sequence A is preferably 10-25 nucleotides, and more preferably, 12-15 nucleotides in length" (see section 5.2.1. and see Figure 5),
>
> "For energy transfer wherein it is desired that the acceptor moiety quench the emissions of the donor, the donor and acceptor moieties are preferably separated by a distance of less than one nucleotide (e.g., on the opposite strand, complementary nucleotides of a duplex structure), although a 5 nucleotide distance (one helical turn) is also advantageous for use" (that is, separated by less than 1 to 5 nucleotide pairs on the double stranded target sequence which is in the range of 0-25 nucleotide pairs, see column 19 lines 35-41); and

(iii) carrying out a denaturation step and at least a selective annealing step in each cycle (taught throughout the patent, see for example column 56 lines 32-38).

Regarding claim 64, Nazarenko et al. teach Thermal cycling was performed using denaturation for 5 min at 94.degree. C., followed by 35 cycles of 30 sec at 95.degree. C. and 2 min 60.degree. C. The PCR was completed with a final 6 min extension at 60.degree. C.

Regarding claim 65, 67, 68, and 69 (a)Nazarenko et al. teach linear and hair-pin primers (see Abstract) and teach the methods using hairpin primers wherein one of the two oligonucleotides of the nucleic acid amplification reaction is labeled with a fluorescent or luminescent signaling moiety kept quenched when the labeled oligonucleotide is not incorporated into the amplification product, the same labeled oligonucletide, when incorporated into the amplification product adapted to generate signal through removal of quenching by separating quencher from the signaling moiety (see column 5 lines 19-41) and teach they remained quenched when not incorporated into amplification (see for example Figure 5, and it is noted that claim 69 provides optional part a, b, and c).

Regarding claims 70-73, Nazarenko et al. teach wherein a first oligonucleotide primer pair selected to amplify a first segment of the target nucleic acid is used at appropriate concentrations, a second oligonuceotide primers with forward and reverse primers selected to amplify a second segment of the first segment at appropriate concentration used in a semi-nested PCR amplification which is a type of nested PCR when the second oligonucleotide primer pair is a duplex of the labeled oligonucleotides labeled with a donor and acceptor (see column 4 lines 1-42).

Further regarding claim 72, Nazarenko et al. teach known amplification procedures (see Abstract and see section *16.2 Methods*).

Further regarding claim 73, Nazarenko et al. teach as noted above and teach amplification teach:

a primer labeled near the 3' end (see R of Fig. 7),

an unlabeled primer (see F of Fig. 7),

a third labeled oligonucleotide (see P of Fig. 7),

where the labeled primer is incorporated into the sequence (see Fig. 7) and where the labels are MET/FRET donor and acceptor and come within the MET distance on the target nucleic acid (as given above and see Fig. 7) the amplification comprising:

adding polymerase, reaction buffer, deoxy nucleoside triphosphates (dNTPs) in addition to the effective amounts of the amplification primers to the samples, cycling the sample between at least a denaturation temperature and an elongation temperature, exciting the reaction mixture with the donor exciting radiation or light, measuring the emission of the acceptor MET moiety (see column 35 lines 46 to column 36 line 61 and see column 38 lines 16-26).

Regarding claim 74 and 75, Nazarenko et al. teach an oligonucleotide labeled with the acceptor is provided in quenched configuration such that the acceptor remains quenched when the acceptor labeled oligonucleotide which is a hairpin structure (see Figures 1A and 1B) is not incorporated into or not hybridized to the amplification product by teaching it is not incorporated into the amplification product (see column 21 lines 7-

14) and is unhybridized to amplification products for which it lack specificity (see column 5 line 37).

Regarding claim 76, Nazarenko et al. teach at least three labeled oligonucleotides where one is quenched (the second oligonucleotide which is hairpin) and is capable of forming a primer dimer (see claims 89 and 93) and teach that

Regarding claim 77a and 78-79, Nazarenko et al. teach a first hairpin oligonucleotide 10 -40 bases line with a stem structure (see Figure 1A and 1B and column 23 lines 1-11) and where the target sequence can be RNA (see column 14 line 33).

Regarding claim 80, Nazarenko et al. teach in situ PCR (see column 14 line 2).

Regarding claims 81 and 84, Nazarenko et al. teach quantitating large numbers of mRNA and cDNA (see column 20 lines 3 and 4) using NASBA (see column 28 line 24).

Regarding claim 82, Nazarenko et al Nazarenko et al. teach as noted above and teach amplification teach:

a primer labeled near the 3' end (see R of Fig. 7),

an unlabeled primer (see F of Fig. 7),

a third labeled oligonucleotide (see P of Fig. 7),

where the labeled primer is incorporated into the sequence (see Fig. 7) and where the labels are MET/FRET donor and acceptor and come within the MET distance on the target nucleic acid (as given above and see Fig. 7)

Regarding claim 83, Nazarenko et al. teach common/universal primers (see column 35 lines 53 and 54).

Regarding claims 87, 88 and 96, Nazarenko et al. teach donors and acceptors of fluorescein, DABCYL (see column 3 lines 3-17), and ethidium bromide (see column 10 line 30 and claim 37) which inherently is an intercalator.

Regarding claim 89, Nazarenko et al. teach biotin and avidin (see column 19 lines 50-57).

Regarding claim 91, Nazarenko et al. teach multiplexing of targets and labels (see column 36 lines 3-9).

Regarding claim 92, Nazarenko et al. teach heterogeneous assays by teaching assays with a wash step (see column 3 line 60) and teaches glass slides (column 56 line 11) and glass supports (see column 17 line 17).

Regarding claim 97, Nazarenko et al. teach the closed tube format (see column 31 lines 30-34).

Regarding claim 110-116, Nazarenko et al. teach heterogenous mutation detection by teaching detection of different, that is heterogenous, mutations with MET labels (see column 7 lines 53 to column 8 line 10) which can be insertions substitutions, deletions, or translocations (see column 20 lines 1-16); using a quenched or unquenched primer (see Figures 1-14) which improves higher sensitivity in a ligase chain reaction (see column 14 line 48 and see colun 56 line 40) further teaching MET/FRET detection as follows:

> "The invention provides a method for detecting or measuring a product of a nucleic acid amplification reaction comprising: (a) contacting a sample

comprising nucleic acids with at least two oligonucleotides, a first one of said oligonucleotides comprising a sequence complementary to a preselected target sequence that may be present in said sample, and said first one and a second of said oligonucleotides being a pair of primers adapted for use in said amplification reaction . . . " (see column 13 lines 27-34),

"In another embodiment, the donor moiety is located on a first oligonucleotide and the acceptor is located on a second oligonucleotide" (see column 16 lines 23-26),

and teaching that the donor and acceptor can be MET moieties and FRET moieties which are a type of MET moieties and teach the MET/FRET distance is 10-100 Angstrom (see column 1 lines 14-16 lines 30-56) which is within the range of 10-80 Angstrom,

and teaching : "The target nucleic acid can be genomic or cDNA or mRNA or synthetic, human or animal, or of a microorganism . . (see column 20 lines 3-5).

The Table below is provided for discussion which follows.

Table 1

100% Sequence Matches for SEQ ID Nos. 19 and 25

SEQ ID NO. 19

```
Application 10516361 and Search Result 20080724_093709_us-10-516-361b-19.rge.

Title:          US-10-516-361B-19
Perfect score:  20
Sequence:       1 ggggtactacagcgccctga 20

RESULT 5
LEIGPAA
LOCUS       LEIGPAA         3105 bp    DNA     linear   INV 26-APR-1993
DEFINITION  L.donovani.
ACCESSION   M60048
VERSION     M60048.1  GI:159334
KEYWORDS    glycoprotein 63.
SOURCE      Leishmania donovani
  ORGANISM  Leishmania donovani
            Eukaryota; Euglenozoa; Kinetoplastida; Trypanosomatidae;
            Leishmania.
REFERENCE   1  (bases 1 to 3105)
```

```
  AUTHORS   Webb,J.R., Button,L.L. and McMaster,W.R.
  TITLE     Heterogeneity of the genes encoding the major surface
glycoprotein
            of Leishmania donovani
  JOURNAL   Mol. Biochem. Parasitol. 48 (2), 173-184 (1991)
   PUBMED   1762629
COMMENT     Original source text: L.donovani DNA.
FEATURES             Location/Qualifiers
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                     /organism="Leishmania donovani"
                     /mol_type="genomic DNA"
                     /db_xref="taxon:5661"
     gene            101. .1873
                     /gene="gp63"
     CDS             101. .1873
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                     /codon_start=1
                     /product="glycoprotein 63"
                     /protein_id="AAA29244.1"
                     /db_xref="GI:159335"

/translation="MSVDSSSTHRHRSVAARLVRLAAAGAAVIAAVGTAAAWAHAGAV

QHRCIHDAMQARVRQSVARHHTAPGAVSAVGLSYVTLGAAPTVVRAANWGALRIAVST

EDLTDSAYHCARVGQRISTRDGRFAICTAEDILTDEKRDILVKYLIPQALQLHTERLK

VRQVQDKWKVTGMGNEICGHFKVPPAHITDGLSNTDFVMYVASVPSEGDVLAWATTCQ

VFSDGHPAVGVINIPAANIASRYDQLVTRVVTHEMAHALGFSVVFFRDARILESISNV

RHKDFDVPVINSSTAVAKAREQYGCGTLEYLEMEDQGGAGSAGSHIKMRNAQDELMAP

ASDAGYYSALTMAIFQDLGFYQADFSKAEEMPWGRNAGCAFLSEKCMEDGITKWPAMF

CNENEVTMRCHTGRLSLGVCGLSSSDIPLPPYWQYFTDPLLAGISAFMDYCPVVVPFG

DGSCAQRASEAGAPFKGFNVFSDAARCIDGAFRPKTTETVTNSYAGLCANVRCDTATR

TYSVQVHGGSGYANCTPGLRVELSTVSSAFEEGGYITCPPYVEVCQGNVQAAKDGGNA
                     AAGRRGPRAAATALLVAALLAVAL"
ORIGIN

  Query Match             100.0%;  Score 20;  DB 12;  Length 3105;
  Best Local Similarity   100.0%;  Pred. No. 6.2;
  Matches   20;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 GGGGTACTACAGCGCCCTGA 20
              ||||||||||||||||||||
Db       1114 GGGGTACTACAGCGCCCTGA 1133
```

SEQ ID NO. 25

From NCBI

```
LOCUS       LEIGPAA           3105 bp    DNA     linear   INV 26-APR-1993
DEFINITION  L.donovani.
ACCESSION   M60048
VERSION     M60048.1  GI:159334
KEYWORDS    glycoprotein 63.
SOURCE      Leishmania donovani
  ORGANISM  Leishmania donovani
            Eukaryota; Euglenozoa; Kinetoplastida; Trypanosomatidae;
            Leishmania.
REFERENCE   1  (bases 1 to 3105)
  AUTHORS   Webb,J.R., Button,L.L. and McMaster,W.R.
  TITLE     Heterogeneity of the genes encoding the major surface
glycoprotein
            of Leishmania donovani
  JOURNAL   Mol. Biochem. Parasitol. 48 (2), 173-184 (1991)
   PUBMED   1762629
COMMENT     Original source text: L.donovani DNA.
FEATURES             Location/Qualifiers
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                     /organism="Leishmania donovani"
                     /mol_type="genomic DNA"
                     /db_xref="taxon:5661"
     gene            101..1873
                     /gene="gp63"
     CDS             101..1873
                     /gene="gp63"
                     /codon_start=1
                     /product="glycoprotein 63"
                     /protein_id="AAA29244.1"
                     /db_xref="GI:159335"

/translation="MSVDSSSTHRHRSVAARLVRLAAAGAAVIAAVGTAAAWAHAGAV

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VRQVQDKWKVTGMGNEICGHFKVPPAHITDGLSNTDFVMYVASVPSEGDVLAWATTCQ

VFSDGHPAVGVINIPAANIASRYDQLVTRVVTHEMAHALGFSVVFFRDARILESISNV

RHKDFDVPVINSSTAVAKAREQYGCGTLEYLEMEDQGGAGSAGSHIKMRNAQDELMAP

ASDAGYYSALTMAIFQDLGFYQADFSKAEEMPWGRNAGCAFLSEKCMEDGITKWPAMF

CNENEVTMRCHTGRLSLGVCGLSSSDIPLPPYWQYFTDPLLAGISAFMDYCPVVVPFG

DGSCAQRASEAGAPFKGFNVFSDAARCIDGAFRPKTTETVTNSYAGLCANVRCDTATR
```

```
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                    AAGRRGPRAAATALLVAALLAVAL"
ORIGIN
       1 cccacacgca cgcgcacacc gccgtgcaca agccctcgcc ctcgccctcg ccgtcgccac
      61 cacaccccac tgcccacagc gcccccgcgc ctgcagagcc atgtccgtcg acagcagcag
     121 cacgcaccgg caccgcagcg tcgccgcgcg cctggtgcgc ctcgcggctg ccggcgccgc
     181 agtcatcgct gctgtcggca ccgcggccgc gtgggcacac gccggtgcgg tgcagcaccg
     241 ctgcatccac gacgcgatgc aggcacgcgt gcggcagtcg gtggcgcgcc accacacggc
     301 ccccggcgcc gtgtccgcgg tgggcctgtc gtacgttact ctcggcgccg cgcccacagt
     361 cgtgcgcgcc gcgaactggg gcgcgctgcg catcgccgtc tccaccgagg acctcaccga
     421 ctccgcctac cactgcgctc gcgtcgggca gcgtattagc acgcgcgatg gccgcttcgc
     481 catctgcacc gccgaggaca tcctcaccga cgagaagcgc gacatcctgg tcaaatacct
     541 catcccgcag gcgctgcagc tgcacacgga gcggctgaag gtgcggcagg tgcaggacaa
     601 gtggaaggtg acgggcatgg gcaacgagat ctgtggccac ttcaaggtgc cgccggcgca
     661 catcaccgat ggcctgagca acaccgactt cgtgatgtac gtcgcctccg tgccgagcga
     721 gggggatgtg ctggcgtggg ccacgacctg ccaggtgttc tctgacggcc atccagccgt
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     901 ccgcatcctg gagagcattt cgaacgttcg gcacaaggac ttcgatgttc ccgtgatcaa
     961 cagcagcacg gcggtggcga aggcgccgca gcagtacggc tgcggcacct tggagtatct
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    1141 catcttccag gacctcggct tctaccaggc ggacttcagc aaggccgagg agatgccgtg
    1201 gggccgaaac gccggctgcg ccttcctcag cgagaagtgc atggaggacg gcatcacgaa
    1261 gtggccggcg atgttctgca atgagaacga ggtgactatg cgctgccaca ccggtcgtct
    1321 cagccttggc gtgtgcggtt tatcctctag cgatattccc ttgccgccgt actggcagta
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    1441 gcccttcggt gatggcagct gcgcgcagcg tgcgtctgaa gcgggcgcac cattcaaagg
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    1801 ggctggtcgc cgtggtccgc gcgccgcggc gacggcgctg ctggtggccg cgctgctggc
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    2101 cgcttggaga ggtgcagcag cgcgcgggag ctgaggggag gaggggtgt cgtgcgcggg
    2161 tgcgcatgcc ttctttcact tccttatttg tcttctattt gttccctgcg acacccgcac
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    2881 gcgctctccg ctctccctcc cccaccacct cccctcgcac cctcccttgc cctctccctg
    2941 tcccctccct ccccagatcc gccaacgcat ccgatcccgc tacaccctct cccccgccca
```

```
     3001 cacgcacgcg cacaccgccg tgcacaagcc ctcgccctcg ccctcgccgt cgccaccaca
     3061 ccccactgcc cacagcgccc ccgcgcctgc agagccatgt ccgtc



>gb|M60048.1|LEIGPAA  L.donovani
Length=3105
 Score = 40.1 bits (20),  Expect = 8e-06
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Minus

Query  1     GTCCTGGAAGATGGCCATGG  20
             ||||||||||||||||||||
Sbjct  1153  GTCCTGGAAGATGGCCATGG  1134
```

Claim Rejections - 35 USC § 103

42. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

43. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

44. Claim 98 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al. as applied to claim 63 above, and further in view of Webb et al. (1993) and Buck et al. (1998).

Nazarenko et al. teach as noted above.

Regarding claim 98, Nazarenko et al. teach rhodamine (see column 2 line 5) which can be used to label a primer.

With regard to claim 98, Nazarenko et al. disclose amplification of DNA with primers designed for amplification and detection as given above.

Nazarenko et al. do not specifically teach SEQ ID NOs: 19 or 25.

Webb et al. expressly disclose the identical nucleic acid sequences presented in SEQ ID NOs: 19 and 25 of the instant disclosure in Accession no. M60048 (see Table 1 above). It is noted that the instant primer sites of SEQ ID NOs: 19 and 25 are contained within the sequence disclosed by Webb et al.

The above described references do not specifically disclose the identical primer sequences of SEQ ID NOs: 19 and 25 primers, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art

compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the Accession no. M60048 and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It

is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

45. Claims 93-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al. as applied to claim 63 above, and further in view of Andersson et al. (United States Patent 6,210,897 issued April 3, 2001) and Chetverin et al. (WO 1993/17126 published 1993 and incorporated by Ansersson et al.).

Nazarenko et al. do not specifically teach a covalent linker but teach the other limitations of claims 93-95 as found above and teach high throughput/multiplex methods (see column 36 lines 3-9).

Regarding claim 93, Andersson et al. teaches attachment of probes/primers to solid supports (column 11 lines 55 and 56) which can be through a covalent linking moiety (column 11 line 15) and detection through FRET (see column 10 line 22) and where solid phase can be the translucent silica or glass polymers as taught by Chetverin et al. (see p. 8, 3rd paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Nazarenko et al. by using linkers to solid supports as suggested by Andersson et al. and Chetverin et al. with a reasonable expectation of success. The motivation to do so is provided by Andersson et al. who teach that methods using the covalently bound probes of Chetverin et al. have enhanced sensitivity (column 11 lines 20 and 21). Thus, the

claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

46. No claim is free of the prior art.

47. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 7:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
/M. S./
Examiner, Art Unit 1637
August 18, 2008

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637